US5492806: Method of determining an ordered sequence of subfragments of a nucleic acid fragment by hybridization of oligonucleotide probes

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Inventor(s): **Drmanac; Radoje T.** , Beograd, Yugoslavia
Crkvenjakov; Radomir B. , Beograd, Yugoslavia

Applicant(s): **Hyseq, Inc.**, Sunnyvale, CA

Issued/Filed Dates: **Feb. 20, 1996** / April 12, 1993 . CC

Application Number: **US1993000045912**

IPC Class: **C12Q 001/70; C12Q 001/68;**

Class: **Current:** 435/006; 435/006;
Original: **435/005;** 435/006; 935/077; 935/078;

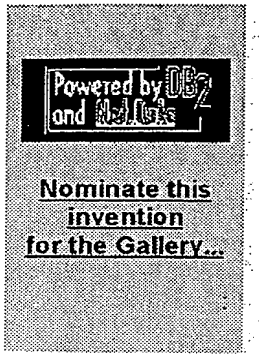
Field of Search: **435/5;6**

Priority Number(s): **YU1987000000570 Family**

Abstract: The sequence of a given nucleic acid fragment is read by the hybridization and assembly of positively hybridizing exactly complementary oligonucleotide probes through overlapping subfragments. By simultaneous hybridization of nucleic acid subfragments bound onto a filter, representing single-stranded phage vector with a cloned insert, with about 50,000 to 100,000 groups of probes, the main type of which is (A,T,C,G)(A,T,C,G)N8(A,T,C,G), information for computer determination of a sequence of DNA having the complexity of a mammalian genome are obtained in one step. To obtain a maximally completed sequence, three libraries cloned into the phage vector, M13, are used. The process can be easily and entirely robotized for factory reading of complex genomic fragments or DNA molecules.

Attorney, Agent, or Firm: **Marshall, O'Toole, Gerstein, Murray & Borun;**

Primary/Assistant Examiners: **Zitomer; Stephanie W.;**



US5525464: Method of sequencing by hybridization of oligonucleotide probes

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Inventor(s): **Drmanac; Radoje T.**, Belgrade, Yugoslavia
Crkvenjakov; Radomir B., Belgrade, Yugoslavia

Applicant(s): **Hyseq, Inc.**, Sunnyvale, CA

Issued/Filed Dates: **June 11, 1996** / Feb. 28, 1994. CC

Application Number: **US1994000203502**

IPC Class: **C12Q 001/68;**

Class: **Current:** 435/091.1; 435/091.2; 435/091.2;
Original: **435/006**; 435/091.1; 435/091.2;

Field of Search: **435/6,91.1,91.2 536/24.33 935/77,78**

Priority Number(s): **YU1987000000570** Family

Abstract: The conditions under which oligonucleotide probes hybridize preferentially with entirely complementary and homologous nucleic acid targets are described. Using these hybridization conditions, overlapping oligonucleotide probes associate with a target nucleic acid. Following washes, positive hybridization signals are used to assemble the sequence of a given nucleic acid fragment. Representative target nucleic acids are applied as dots. Up to to 100,000 probes of the type (A,T,C,G)(A,T,C,G)N8(A,T,C,G) are used to determine sequence information by simultaneous hybridization with nucleic acid molecules bound to a filter. Additional hybridization conditions are provided that allow stringent hybridization of 6-10 nucleotide long oligomers which extends the utility of the invention. A computer process determines the information sequence of the target nucleic acid which can include targets with the complexity of mammalian genomes. Sequence generation can be obtained for a large complex mammalian genome in a single process.

Attorney, Agent, or Firm: **Marshall, O'Toole, Gerstein, Murray & Borun;**

Primary/Assistant Examiners: **Fleisher; Mindy B.**; Ketter; James

- (d) washing the duplex;
- (e) detecting oligonucleotides positively hybridizing as part of said duplex; and
- (f) compiling a sequence of the target nucleic acid from overlapping positively-hybridizing oligonucleotides.

This is a continuation of U.S. application Ser. No. 08/048,152, filed Apr. 15, 1993, now abandoned, which is a continuation of U.S. application Ser. No. 07/576,559, filed Aug. 31, 1990, now abandoned, in turn a continuation-in-part of U.S. application Ser. No. 07/175,088, filed Mar. 30, 1988, now abandoned. Applicants claim priority under 35 U.S.C. § 119 of Yugoslavian Application No. P-570/87 filed Apr. 1, 1987 and Yugoslavian Application No. 18617-P 570/87 filed Sep. 18, 1987, certified copies of which were submitted in the parent application Ser. No. 07/175,088.

Foreign References:

Publication	Country	Date	IPC Class
EP00152886	European Patent Office (EPO)	8 /1985	
DE03506703	Germany	10 /1986	
WO08801302	World Intellectual Property Organization (WIPO)	2 /1988	
WO08910977	World Intellectual Property Organization (WIPO)	11 /1989	
WO09003382	World Intellectual Property Organization (WIPO)	4 /1990	
WO09004652	World Intellectual Property Organization (WIPO)	5 /1990	

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US5667972: Method of sequencing of genoms by hybridization of oligonucleotide probes

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Inventor(s): **Drmanac; Radoje T.** , Beograd, Yugoslavia
Crkvenjakov; Radomir B. , Beograd, Yugoslavia

Applicant(s): **Hyseg, Inc.**, Sunnyvale, CA

Issued/Filed Dates: **Sept. 16, 1997** / June 5, 1995

Application Number: **US1995000461106**

IPC Class: **C12Q 001/68; C07H 021/04;**

Class: **Current:** 536/023.1; 536/023.1;
Original: **435/006;** 536/023.1; 935/077; 935/078;

Field of Search: **435/006 536/23.1 935/77,78**

Priority Number(s): **YU1987000000570 Family**

Abstract: The conditions under which oligonucleotides hybridize only with entirely homologous sequences are recognized. The sequence of a given DNA fragment is read by the hybridization and assembly of positively hybridizing probes through overlapping portions. By simultaneous hybridization of DNA molecules applied as dots and bound onto a filter, representing single-stranded phage vector with the cloned insert, with about 50,000 to 100,000 groups of probes, the main type of which is (A,T,C,G)(A,T,C,G)N8(A,T,C,G), information for computer determination of a sequence of DNA having the complexity of a mammalian genome are obtained in one step. To obtain a maximally completed sequence, three libraries are cloned into the phage vector, M13, bacteriophage are used: with the 0.5 kb and 7 kbp insert consisting of two sequences, with the average distance in genomic DNA of 100 kbp. For a million bp of genomic DNA, 25,000 subclones of the 0.5 kbp are required as well as 700 subclones 7 kb long and 170 jumping subclones. Subclones of 0.5 kb are applied on a filter in groups of 20 each, so that the total number of samples is 2,120 per million bp. The process can be easily and entirely robotized for factory reading of complex genomic fragments or DNA

US5525464	6 /1996	Drmanac et al.	Method of sequencing by hybridization of oligonucleotide probes

First Claim: Show all 7 claims

We claim:

1. A method of determining the sequence of an ambiguous locus in a nucleic acid fragment in a sequencing by hybridization process, said method comprising:

- (a) prehybridizing said nucleic acid fragment with an excess of unlabeled first oligonucleotide probe which is exactly complementary to one possible sequence at said ambiguous locus;
- (b) competitively hybridizing said nucleic acid fragment with a labeled second oligonucleotide probe which is exactly complementary to a second possible sequence at said ambiguous locus;
- (c) detecting whether the labeled second oligonucleotide probe hybridizes, thereby determining the sequence of said ambiguous locus in said nucleic acid fragment.

This is a continuation of U.S. application Ser. No. 045,912, filed Apr. 12, 1993, now U.S. Pat. No. 5,492,806; which is a continuation of U.S. application Ser. No. 07/723,712 filed Jun. 18, 1991, now U.S. Pat. No. 5,202,231; which is a continuation of U.S. application Ser. No. 07/175,088 filed Mar. 30, 1988 now abandoned; which is based on Yugoslavian No. P-570/87 filed on Apr. 1, 1987.

Foreign References:

Publication	Country	Date	IPC Class
EP00152886	European Patent Office (EPO)	8 /1985	
EP00197266	European Patent Office (EPO)	10 /1986	
DE03506703	Germany	10 /1986	
WO08801302	World Intellectual Property Organization (WIPO)	2 /1988	
WO08910977	World Intellectual Property Organization (WIPO)	11 /1989	
WO09003382	World Intellectual Property Organization (WIPO)	4 /1990	
WO09004652	World Intellectual Property Organization (WIPO)	5 /1990	

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- Wallace et al., "The use of synthetic oligonucleotides as hybridization probes. II. Hybridization of oligonucleotides of mixed sequence to rabbit ß-globin DNA," Nucleac Acids Research, 9:879-894 (1981).
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— Hyseq

US5695940: Method of sequencing by hybridization of oligonucleotide probes

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Inventor(s): **Drmanac; Radoje T.**, Beograd, Yugoslavia
Crkvenjakov; Radomir B., Beograd, Yugoslavia

Applicant(s): **Hyseq, Inc.**, Sunnyvale, CA

Issued/Filed Dates: **Dec. 9, 1997** / June 5, 1995

Application Number: **US1995000460853**

IPC Class: **C12Q 001/68;**

Class: **Current:** 536/023.1; 536/024.33; 536/024.33;
Original: **435/006;** 536/023.1; 536/024.33;

Field of Search: **435/6,91.1,91.2 536/24.33**

Priority Number(s): **YU1987000000570** **Family**

Abstract: The conditions under which oligonucleotide probes hybridize preferentially with entirely complementary and homologous nucleic acid targets are described. Using these hybridization conditions, overlapping oligonucleotide probes associate with a target nucleic acid. Following washes, positive hybridization signals are used to assemble the sequence of a given nucleic acid fragment. Representative target nucleic acids are applied as dots. Up to to 100,000 probes of the type (A,T,C,G) (A,T,C,G)N8(A,T,C,G) are used to determine sequence information by simultaneous hybridization with nucleic acid molecules bound to a filter. Additional hybridization conditions are provided that allow stringent hybridization of 6-10 nucleotide long oligomers which extends the utility of the invention. A computer process determines the information sequence of the target nucleic acid which can include targets with the complexity of mammalian genomes. Sequence generation can be obtained for a large complex mammalian genome in a single process.

Attorney, Agent, or Firm: **Marshall, O'Toole, Gerstein, Murray & Borun;**

Primary/Assistant Examiners: **Ketter; James;**

We claim:

1. A method of sequencing a target nucleic acid of unknown sequence comprising the steps of:

- (a) using conditions which differentiate an exactly complementary oligonucleotide probe and an oligonucleotide probe having a single mismatched nucleotide;
- (b) contacting a plurality of oligonucleotides, each from six to ten nucleotides in length, with said target nucleic acid;
- (c) forming a duplex between the target nucleic acid and the plurality of oligonucleotides;
- (d) washing the duplex;
- (e) detecting oligonucleotides positively hybridizing as part of said duplex; and
- (f) compiling a sequence of the target nucleic acid from overlapping positively-hybridizing oligonucleotides.

This is a Continuation of U.S. application Ser. No. 08/203,502, filed Feb. 28, 1994, now U.S. Pat. No. 5,525,464; which in turn is a File-Wrapper Continuation of U.S. application Ser. No. 08/048,152, filed Apr. 15, 1993, now abandoned, which is a continuation of Ser. No. 07/576,559, filed Aug. 31, 1990, now abandoned, which is a continuation-in-part of application Ser. No. 07/175,088 filed Mar. 30, 1988, now abandoned, which is incorporated by reference herein in its entirety. Applicants claim priority under 35 U.S.C. §119 of Yugoslavian Application No. P-570/87 filed Apr. 1, 1987 and Yugoslavian Application No. 18617-P 570/87 filed Sep. 18, 1987, certified copies of which were submitted in the parent application Ser. No. 07/175,088.

Foreign References

Publication	Country	Date	IPC Class
EP00152886	European Patent Office (EPO)	8 /1985	
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WO09004652	World Intellectual Property Organization (WIPO)	5 /1990	

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